COMMENTARY

Fundamental sex difference in human brain architecture

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In PNAS, a report by Ingalhalikar et al. (1) has the makings of a landmark paper. Here I would like to briefly suggest why.

Biomedical research in general, and neuroscience in particular, has been built on a false assumption. I refer to the assumption that one may safely ignore potential sex influences, for essentially every domain outside sexual functions and sex-specific issues like prostate function, and still learn everything fundamental there is to learn. Widespread acceptance of this false assumption among neuroscientists is the reason they still overwhelmingly use only males in their animal experiments while implying that their results will apply equally to females and why potential sex influences are still routinely ignored or dismissed even when both sexes are studied, as in many human subject and knockout mouse studies.

Sex Matters

However, even if it was once scientifically defensible to assume that sex does not matter to brain function, it is no longer. The reason is simple: we now know that sex influences—small to medium to large—are extremely widespread on brain function. The validity of the assumption that the sex of subjects cannot powerfully alter, negate, and even reverse findings (hence, conclusions) has been crushed under the weight of evidence proving that it can and regularly does and at every level of investigation down to genes, single neurons, and even ion channels (2).

For neuroscientists cognizant of this striking development, the main challenge now is to better understand the dizzying plethora of sex influences being uncovered. Males and females appear to be two complex mosaics, similar in some respects, mildly to highly different in others (3). This state of affairs raises the question: are there more primary, or fundamental, sex influences at work, influences out of which many other sex effects may arise? It is in the search for the potentially more fundamental neural sex differences that the paper by Ingalhalikar et al. finds its importance.

These investigators used a form of MRI called diffusion tensor imaging (DTI) to examine the patterns of white matter (the wires connecting the gray matter, referred to by the authors as the structural connectome) in an extremely large sample of youths (ages 8–22; 428 males and 521 females). The sample size alone places this study in rare human brain imaging company, greatly enhancing confidence in the solidity of the conclusions. Very few MRI studies have anything resembling the power of this study. Such power is an especially valuable trait for the issue of sex differences in human brain anatomy, because they are unfairly viewed by many neuroscientists as unreliable and hence not of much importance. In my experience over the last decade working on the sex influence issue, I have found that neuroscientists unaware of the literature overwhelmingly refer to uncertainties regarding sex differences in the size/shape of the corpus callosum to argue that sex differences in human brain anatomy are unreliable. However, of course this is completely unfair. In fact, as should be expected in any large domain of investigation, sex differences in brain anatomy vary in size from the small to the huge. For example, Kovalev et al. (4) found extremely large sex differences in the "texture" of white matter (an index of the orderliness of fibers within the tracts). It makes no more sense to conclude on the basis of the findings of Kovalev et al. that all anatomical sex differences in the human brain are extremely large than it does to conclude on the basis of arguments about the corpus callosum that they are all small and unreliable.

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Different Wiring Patterns

In fact, Ingahalikar et al., using a number of different methods of analysis, report clear and striking sex differences. Most notably, the brains of men exhibit a far smaller degree of interconnectedness, both within and across the hemispheres, than do those of women, which, conversely, exhibit a significantly greater degree of interconnectedness both across the hemispheres and across lobes within a hemisphere. Essentially, men's brains on average appear wired for more localized, modular function compared with those of women, whose brains on average appear wired for more connectionist, cross-module function.

This neuroanatomical conclusion is striking, as it appears to dovetail nicely with one of, if not the, most consistently supported principle in the literature regarding human sex differences, namely, that the brains of men tend to be more asymmetrically organized across the two hemispheres than are those of women, as documented in numerous reviews (5–7). Ingalhalikar et al. now give this well-established sex difference a very plausible anatomical basis.

Other aspects of the findings are intriguing, if more puzzling, at least at first blush. For example, developmentally, the authors detected no age × sex interaction in their analysis, suggesting that there are no reliable sex differences in the developmental trajectory of the connectivity patterns, although others have seen striking sex differences in developmental trajectories of some aspects of human brain anatomy (8). Also intriguing is the fact that the general pattern of results appears reversed in the cerebellum alone, a curious fact certainly deserving of greater attention in future work.

A comedian discussing men and women once described the male brain as a bunch of boxes that don't touch one another and the female brain as a complex ball of interconnected wires. Amusing as the bit was, the

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analogies may be more apt than he could have known. The findings of Ingahalikar et al. do indeed point to a greater degree of modular function in the physical architecture of the male brain and of interconnectedness in physical architecture of the female brain. Given the size of the study, the consistency of the conclusions across various analytic approaches, and the seeming concordance of key findings with well-established literature addressing brain function, one cannot fairly accuse Ingalhalikar et al. of hyperbole when they claim that their findings "reveal fundamental sex differences in the architecture of the human brain." Theirs is a landmark paper that should accelerate acceptance of the notion that, for those who want to understand how brains function, sex matters.

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3 Cahill L (2006) Why sex matters for neuroscience. *Nat Rev Neurosci* 7(6):477–484.

4 Kovalev VA, Kruggel F, von Cramon DY (2003) Gender and age effects in structural brain asymmetry as measured by MRI texture analysis. *Neuroimage* 19(3):895–905.

5 McGlone J (1980) Sex differences in human brain asymmetry: A critical survey. *Behav Brain Sci* 3(2):215–263.

6 Voyer D (1996) On the magnitude of laterality effects and sex differences in functional lateralities. *Laterality* 1(1):51–83.

7 Hiscock M, Perachio N, Inch R (2001) Is there a sex difference in human laterality? IV. An exhaustive survey of dual-task interference studies from six neuropsychology journals. *J Clin Exp Neuropsychol* 23(2):137–148.

8 Lenroot RK, et al. (2007) Sexual dimorphism of brain developmental trajectories during childhood and adolescence. *Neuroimage* 36(4):1065–1073.